SHORT COMMUNICATION

Tetracycline Resistant Cholera in Kelantan

K Ranjit, MPH*, M Nurahan, M. Path, *Epidemiology Unit, Department of Health Kelantan, Wisma Persekutuan, Jalan Bayam, Kota Bharu **Department of Pathology, Hospital Kota Bharu, Kelantan**

Summary

Sensitivity testing on *Vibrio cholerae* isolates during an epidemic in 1998 in Kelantan identified strains resistant to tetracycline. This prompted a change in the usual management of cholera in Kelantan. The antibiotic of choice was changed from tetracycline to erythromycin.

Key Words: Cholera, Tetracycline, Resistance

Introduction

The 1998 cholera outbreak in Kelantan occurred from February to August, and affected eight of the ten districts, namely, Tumpat, Kota Bharu, Bachok, Gua Musang, Pasir Mas, Kuala Krai, Tanah Merah and Jeli. A total of 146 cases and 184 carriers were detected. A case is defined when *Vibrio cholera* are isolated in stools by microscopy or culture in a person complaining of diarrhoea. A carrier is one without discernible disease but in whom the organism has been identified.

Tetracycline (doxycycline) is generally the antibiotic of choice in the treatment and prophylaxis of cholera in Malaysia. In Hospital Kota Bharu, sensitivity testing of *Vibrio cholerae* isolates is done regularly on some of the isolates. The practice of the Pathology Department is that sensitivity testing is only done in a proportion of cases as an outbreak is assumed to usually stem from a common source. In 1992, sixteen isolates (of 37 cases) tested were all sensitive to tetracycline; while the following year, 8.9% of 112 isolates tested were resistant. In 1994 all eight isolates tested (from a total of 23 cases) were fully sensitive. Between 1995 and 1997 there were no indigenous cases of cholera in Kelantan, however there were 17 cases in 1996 which were linked to the major outbreak in Pulau Pinang. Sensitivity testing was however not done in these cases (from Pulau Pinang).

Report of sensitivity testing

During the 1998 outbreak, about 200 patients were admitted with moderate to severe diarrhoea, of which 146 were microbiologically confirmed. The Department of Pathology at Hospital Kota Bharu was alerted by treating physicians regarding the prolonged duration of illness in some of the cases. The average duration of hospitalisation was 9.7 days (range 3 to 42 days). This prompted sensitivity testing which revealed that 33.3% of the isolates tested (8/24) were definitely resistant to tetracycline, while another 54.2% (13/24) demonstrated an intermediate result. Only 12.5% (3/24) isolates of *Vibrio cholerae* were indeed sensitive to tetracycline. Sensitivity testing was performed by the "disc diffusion method" using the Guidelines of the National Committee for Clinical Laboratory Standards. An isolated organism is said to be resistant if it is not killed or inhibited by the usual concentration of antibiotic. The sensitivity pattern as reported to the State Health Department is as shown in Table I.

Erythromycin sensitivity was not tested for. Therefore the antibiotics that could be used were ciprofloxacin (100% sensitivity) and ampicillin (87.5% sensitivity). This was the situation at about the 22nd epidemiological week of the outbreak. By this time 132 cases and 157 carriers had already been detected and the outbreak was still not under control. Considering the

Table I
Sensitivity Pattern of *Vibrio Cholerae* Isolates, Kelantan 1998

Antibiotic	Sensitive	Intermediate	Resistant
Tetracycline	12.5% (3/24)	54.2% (13/24)	33.3% (8/24)
Cotrimoxazole	8.3% (2/24)	0	91.7% (22/24)
Chloramphenicol	20.8% (5/24)	66.6% (16/24)	12.5% (3/24)
Ampicillin	87.5% (21/24)	8.33% (2/24)	4.17% (1/24)
Streptomycin	8.83% (2/24)	0	91.67% (22/24)
Kanamycin	100% (24/24)		
Gentamicin	100% (11/11)		
Carbenicillin	100% (11/11)		
Cephalothin	100% (11/11)		
Ciprofloxacin	100% (11/11)		

Source: Pathology Department, Hospital Kota Bharu

situation prevalent at the time, the state technical committee arrived at the following decisions:

- The sensitivity pattern was to be monitored on a regular basis by the Hospital Kota Bharu laboratory on all *Vibrio cholerae* isolates.
- Sensitivity pattern for erythromycin was to be tested.
- All adult cases and carriers were to be treated (while awaiting erythromycin sensitivity results) with ciprofloxacin 1 gram stat orally.
- Cases and carriers below 18 years were to be treated with ampicillin as the sensitivity rate was 87.5%.
- No mass chemoprophylaxis was allowed.
- Close contacts were to be given prophylaxis with bacampicillin, 400 mg orally, twice daily for five days, or until the rectal swab results were known.
- Prophylaxis for food handlers was to be limited to only those with a clear epidemiological link to a known case.

Discussion

The use of antibiotics in the treatment of cholera although not essential, is effective in reducing the volume of diarrhoea in patients with severe cholera and shortens the period during which *Vibrio cholera 01* is excreted[1]. In addition it usually stops the diarrhoea within 48 hours, thus shortening the period of hospitalization. The W.H.O. recommends that antibiotics be used only in the treatment of severely dehydrated cases. Generally, doxycycline or tetracycline is the preferred antibiotic, however if there is a problem of resistance a suitable substitute should be identified by sensitivity testing[2].

The W.H.O. does not support mass chemoprophylaxis and recommends that selective chemoprophylaxis be considered only when surveillance shows that at least one household member in five becomes ill after the first case has been reported[2]. In field practice however, this recommendation is usually modified and chemoprophylaxis is quite often extended beyond the household to the surrounding neighborhood, and in some instances even to the entire village. This can result in the emergence of resistant strains, thus depriving ill patients of a valuable aid in treatment.

In the 1998 outbreak in Kelantan, the ratio of case (146) to carrier (184) was 0.8:1. Chemoprophylaxis with doxycycline was administered to 12,128 people (10,046 contacts and 2082 food handlers). This ingrained, although incorrect practice of mass chemoprophylaxis may have contributed to the emergence of tetracycline resistant *Vibrio cholera 01* strains in this part of the country.

Elsewhere, resistant strains have been identified in Indonesia, Philippines, India, Bangladesh and Africa. The Tanzanian cholera epidemic in 1978 highlighted

that all isolates during the first month after the disease was recognised were fully sensitive to tetracycline, but 76% of isolates were resistant after five months of extensive therapeutic and prophylactic use[3]. This finding reiterates the fact that mass chemoprophylaxis in the control of cholera should be discouraged as it is a major factor in the emergence of resistant strains. These antibiotic resistant strains in turn result in a longer duration and larger volume of diarrhoeal stools resulting in prolonged hospitalization[4]. In line with this both hospital and community control measures need to be instituted for a longer period of time - which translates into increased cost of controlling the outbreak.

In Kelantan, with the detection of tetracycline resistant strains, adults above 18 years were treated with a single dose of ciprofloxacin (while awaiting sensitivity results for erythromycin). The drug was 100% sensitive, and single dose ciprofloxacin is known to be effective in the treatment of cholera caused by *Vibrio cholerae 01* or *0139*. It is superior to single dose doxycycline in the eradication of *Vibrio cholerae* from the stool, and is the preferred treatment in areas where tetracycline resistant *Vibrio cholerae* are common[5]. The drug was not used for cases aged under 18 years, or in pregnant or nursing women as the drug is contraindicated in these groups. Subsequent testing however yielded 100% sensitivity to erythromycin, the drug which is now the antibiotic of choice in the management of cholera in Kelantan.

Substitution of one first line drug (tetracycline) with another (erythromycin) has in this case escalated the cost of treating cholera by 11.7 times (from RM 0.2 to RM 2.34) per patient. The newer generation drugs should be reserved for certain pressing situations only, as in addition to the added cost, there is the risk of emergence of resistant strains. Routine sensitivity testing for all strains and rational antibiotic usage are therefore key strategies in combating the problem of antibiotic resistance.

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